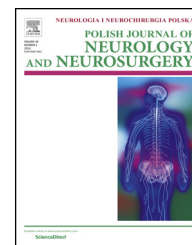


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Original research article

Suicidality and its determinants among Polish patients with epilepsy



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ABSTRACT

Background and purpose: The aim of this study was to evaluate the prevalence of suicidal ideation among Polish patients with epilepsy and to assess the potential determinants of suicidality in this cohort.

Material and methods: The study comprised 301 patients with epilepsy seen in the tertiary epilepsy clinic. Patients' characteristics included demographic variables, epilepsy-related variables, as well as occurrence of comorbidities, ongoing use of any other medications, family history of epilepsy and/or depression. Beck Depression Inventory (BDI) was used to assess depressive symptoms, and question no. 9 of BDI was specifically used to reveal suicidality.

Results: Mean age of subjects was 35.5 years. 113 (37.5%) had frequent seizures and 96 patients (31.9%) had remission. BDI score > 11 points (suggestive for depression) was found in 127 subjects. Suicidal ideation has been revealed in 30 (10.0%) out of 301 studied patients. Patients with suicidal ideation were older and more commonly reported frequent seizures. Almost all of them (93.3%) had clinically significant depressive symptoms (BDI score > 11). Multivariate analysis revealed that severity of depressive symptoms (OR = 1.16 per one-point increase in BDI score, 95% CI: 1.10–1.22, $p < 0.001$) and the use of potentially depressogenic medication (OR = 3.04, 95% CI: 1.04–8.89, $p = 0.04$) were independent determinants of suicidality among studied patients.

Conclusions: Suicidal ideations were revealed by about 10% of studied epileptic patients who visited tertiary center for epilepsy. Independent predictors of suicidality among studied patients included depression itself and the use of potentially depressogenic medication.

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1. Introduction

The risk of suicide is about three times higher among patients with epilepsy than in general population [1,2]. Psychiatric comorbidities, such as depression or anxiety, are also more common among epileptic patients [3,4] and the association between the presence of psychiatric illness and suicide is well established [5]. It comes as no surprise, therefore, that the suicidality among patients with epilepsy is often attributed to psychiatric disorders.

Recent population-based studies suggest, however, that the risk of suicide in those patients cannot be fully explained by the coexistence of psychiatric morbidities [1]. Some other factors inherent to the epilepsy or its management can play significant role as well, as exemplified by the FDA warning about the increased risk of suicidal ideation and suicidal behavior in people treated with antiepileptic drugs (AEDs) [6]. Other potential risk factors for suicide among epileptic patients included AED polytherapy or high seizure frequency [7]. Patients newly diagnosed with epilepsy are also at higher risk of suicide while more advanced age seems to be associated with the decreasing risk of suicide [1].

Some recent studies suggest also bidirectional association between depression or suicidal ideation and epilepsy, pointing to the potential common mechanisms that both increase the risk of depression/suicidality and decrease the threshold for seizures [8] which might favor the presence of unrecognized biological determinant of the suicidality among those patients.

Suicidality in general population is related also to various sociodemographic and cultural features. Thus, the generalization of findings obtained in different countries is limited and justifies the more local approach to that issue. EZOP-Polska was the only methodologically sound epidemiological study aimed at the evaluation of prevalence of psychiatric disorders in Poland [9]. According to this survey, previous suicidal attempts were reported by 0.7% of both women and men aged 18–64 [10]. Data related specifically to epileptic patients are scarce; a single study carried out in 1970s in Poland reported that 7.3% of deaths among epileptic patients in Warsaw was due to suicide [11] but no data are available on potential risk factors related to suicide among Polish patients with epilepsy.

Accordingly, we have designed this study to evaluate the rate of suicidal ideation among Polish patients with epilepsy, and, consequently, to assess the potential determinants of suicidality in this cohort.

2. Materials and methods

2.1. Patients

This study comprised 301 consecutive patients seen in the tertiary epilepsy clinic in university hospital.

All subjects had epilepsy diagnosed and classified according to the International League Against Epilepsy guidelines and classifications [12,13]. The other inclusion criterion was brain imaging with magnetic resonance imaging (or, rarely, computed tomography if magnetic resonance imaging was contraindicated) performed within 5 years preceding the

inclusion to this study. The present paper deals with the suicidality and its determinants, while data related to depression in the slightly smaller sample of those patients were published previously [14].

Patients were excluded if they were diagnosed with concomitant psychogenic non-epileptic seizures or if they suffered from tonic, atonic, clonic or atypical absence seizures. We also excluded subjects with some significant comorbidities such as malignancies, neurodegenerative diseases or other progressive neurological disorders, as well as patients with current hyper- or hypothyroidism (as suggested by the abnormal serum thyroxine). Any change in type or dose of AED(s) within one month preceding the latest visit in an out-patient clinic also precluded the participation in the study as did the drug or alcohol abuse. Finally, patients with Mini-Mental State Examination score < 24 (suggestive for cognitive impairment) were also excluded.

Our study protocol observed the principles of Helsinki Declaration and was approved by the university bioethical committee. The detailed information about the aims and methods of the study was provided to each participant. Each subject signed an informed consent to participate.

2.2. Protocol

All procedures required specifically for this cross-sectional study were performed during routine visits in out-patient clinic. Also, we have retrieved data from patients' medical files.

Medical history was obtained with the use of the questionnaire which comprised information on age, sex, marital status, vocational activity, etiology and duration of epilepsy, type and frequency of seizures, ongoing treatment with AED(s), occurrence of comorbidities, ongoing use of any other medication(s), family history of epilepsy and/or depression. Additionally, each patient underwent neurological examination to reveal any focal or global signs of brain damage.

Medical history, EEG or video-EEG and neuroimaging were all used to classify epileptic seizures and epileptic syndromes according to the International Classification of Seizures [13,15] and International Classification of Epilepsies and Epileptic Syndromes [16]. Seizures were divided into focal (with or without alterations of alertness/consciousness as well as focal seizures transformed into bilateral convulsive seizures), generalized (tonic-clonic, typical absences or myoclonic seizures) or unclassified seizures (if information from different sources was discordant in regard of seizure characteristics). Epileptic syndromes were classified into localization-related, generalized or of unknown onset.

All patients used seizure diaries before entering the study as an essential part of the management. Frequency of seizures in the year preceding the inclusion to this study was recorded from seizure diaries and dichotomized into frequent (at least one per month) or rare seizures (less than one per month). Complete remission was defined as being seizure-free for the last year.

The ongoing treatment with antiepileptic drugs (AED) was recorded according to the information provided by the patient, and supplemented with the data from medical records.

Patients self-assessed their potential depressive symptoms with the use of Polish version of revised Beck Depression Inventory (BDI); the assessment was performed at least 72 h

after the last seizure (to avoid post-seizure depressive symptoms) and patients evaluated their depressive symptoms occurring within one week preceding the assessment. The first version of BDI was validated previously in Polish population and the cut-off score of 12 points was indicated as the value suggestive for depression [17]. In the present study, we used question no. 9 of BDI (suicidal thoughts or wishes) to reveal potential suicidal thoughts, ranging from 0 ('I don't have any thoughts of killing myself') to 3 ('I would kill myself if I had the chance').

Information on comorbidities, including psychiatric ones, and treatment with drugs other than AEDs, including antidepressants, was collected during interview and confronted with the medical records. We noted the presence of chronic illnesses, including arterial hypertension, ischaemic heart disease, history of myocardial infarction, diabetes, hypercholesterolaemia, asthma, as well as corrected hypo- or hyperthyreosis. All medications taken within 3 months preceding the study visit were recorded, with the special focus on the drugs with the potential depression-induction properties. The list of potentially depressogenic medications was set according to the literature [18] and originally included hormones (corticosteroids, estrogens, progesterone), β -blockers (mostly propranolol), calcium antagonists (flunarizine), some antiparkinsonian drugs (levodopa, amantadine), and interferons.

Family history of epilepsy and/or depression was established in interview with the patient or his/her proxies.

2.3. Statistical analysis

Qualitative variables were characterized with numbers and percentages. Quantitative variables were described with the use of a mean and standard deviation (SD). Chi-square test (or Fisher exact test, where appropriate) was used to assess the significance of the differences between the qualitative data. Student t-test was used to assess differences between quantitative variables.

Initially, univariate analysis of factors that differed between patients with and without suicidality was made. Then, analysis of independent factors that influenced the presence of suicidality (dependent variable) was performed by logistic regression modeling. Initial model was built with all the variables that differed at the level of $p < 0.2$ in univariate analysis. Models were created using stepwise method (backward selection with determining criterion likelihood ratio for variables selection). A p -value of less than 0.05 was considered statistically significant for variables in the final model. All the analyses were performed using Statistica v. 10 (StatSoft Inc., Tulsa, OK).

3. Results

We have studied 301 patients, including 180 women (59.8%).

Mean age of subjects was 35.5 years (SD: 14.8). Mean age at onset of epilepsy was 20.9 years (SD: 15.2), and mean duration of the disease was 14.7 years (SD: 11.3). Idiopathic generalized epilepsy was diagnosed in 66 (21.9%) patients, 195 (64.8%) had focal epilepsy, and further 40 subjects (13.3%) had unclassified epilepsy. One hundred and thirteen patients (37.5%) had frequent seizures (i.e. more often than monthly), and 96 patients (31.9%) had remission (no seizures within the previous year). BDI score > 11 points (suggestive for depression) was found in 127 subjects (42.2%). Thirty-five patients (11.6%) used potentially depressogenic medications. Monotherapy with AED was used in 167 subjects (55.5%).

Suicidal ideation has been revealed in 30 (10.0%) out of 301 studied patients. Twenty-nine of them scored '1' in BDI item no. 9, and the further one subject scored '2'. Thus, we did not discern patients with different scores in that item in all analyses.

Table 1 provides details of comparison between patients with and without suicidal ideation regarding demographic variables and concomitant disorders. Patients with suicidal ideation were older and women constituted greater proportion

Table 1 – Comparison of demographic factors and comorbidities between epileptic patients with or without suicidal ideation (univariate analysis). Data shown as n (%) or mean with standard deviation.

Variable	Suicidal ideation (n = 30)	No suicidal ideation (n = 271)	p-Value for the difference
Age	41 (16.2)	34.9 (14.6)	0.035
Sex (% of women)	19 (63.3%)	161 (59.4%)	0.017
Marital status (% of living alone)	13 (43.3%)	164 (60.5%)	0.07
Education level			
Primary school	5 (16.7%)	28 (10.3%)	0.22
Vocational school	6 (20.0%)	56 (20.7%)	0.93
High school	10 (33.3%)	137 (50.6%)	0.07
College	9 (30.0%)	50 (18.5%)	0.13
Occupational activity (% of active)	7 (23.3%)	106 (39.1%)	0.09
Comorbidities			
Arterial hypertension	5 (16.7%)	35 (12.9%)	0.37
Diabetes	0	7 (2.6%)	0.30
Ischaemic heart disease	2 (6.7%)	9 (3.3%)	0.34
History of myocardial infarction	1 (3.3%)	3 (1.1%)	0.30
Hypercholesterolaemia	2 (6.7%)	17 (6.3%)	–
Asthma	0	7 (2.6%)	
Hypothyreosis	0	4 (1.5%)	
Hyperthyreosis	0	5 (1.8%)	

Table 2 – Comparison of epilepsy characteristics between epileptic patients with or without suicidal ideation (univariate analysis). Data shown as n (%) or mean with standard deviation.

Variable	Suicidal ideation (n = 30)	No suicidal ideation (n = 271)	p-Value for the difference
Age at onset of epilepsy	25.8 (17.4)	20.3 (14.9)	0.06
Disease duration	15.0 (12.3)	14.6 (11.2)	0.85
Family history of epilepsy	6 (20%)	63 (23.2%)	0.68
Type(s) of seizures			
Simple partial	6 (20.0%)	42 (15.6%)	0.53
Complex partial	15 (50.0%)	118 (43.5%)	0.50
Secondary generalized	20 (66.7%)	144 (53.1%)	0.16
Absence	4 (13.3%)	29 (10.7%)	0.42
Myoclonic	3 (10.0%)	25 (9.2%)	0.55
Primary generalized	4 (13.3%)	59 (21.8%)	0.20
Unclassified	2 (6.7%)	34 (12.5%)	0.27
Treatment ^a			
Valproate	16 (53.3%)	164 (60.5%)	0.45
Carbamazepine	5 (16.7%)	58 (21.4%)	0.37
Phenobarbital	1 (3.3%)	9 (3.3%)	0.66
Phenytoin	1 (3.3%)	7 (2.6%)	0.57
Clonazepam	3 (10.0%)	7 (2.6%)	0.066
Lamotrigine	6 (20.0%)	33 (12.2%)	0.23
Topiramate	6 (20.0%)	34 (12.5%)	0.25
Levetiracetam	9 (30.0%)	63 (23.2%)	0.41
Gabapentin	1 (3.3%)	14 (5.2%)	0.55
Oxcarbazepine	6 (20.0%)	33 (5.2%)	0.23
Monotherapy	12 (40.0%)	155 (57.2%)	0.07
Frequent seizures (>1/month)	19 (63.3%)	94 (34.7%)	0.002
No seizures in the previous year	5 (16.7%)	91 (33.6%)	0.042

^a Other antiepileptic drugs (primidone, vigabatrin, tiagabine, ethosuximide, clobazam) were used by less than 3% of patients in each group.

among subjects with suicidality, but otherwise no demographic factor distinguished those two groups.

The only factor related to epilepsy that differed significantly between patients with or without suicidal ideation was frequency of seizures, with greater proportion of patients with frequent seizures among patients reporting suicidality (Table 2). Suicidality was reported by 4 out of 66 patients with primary generalized epilepsy (6.0%) and by 24 out of 195 patients with focal epilepsy (12.3%) ($p = 0.16$).

Patients with suicidal ideation significantly more often had history of depression and they used antidepressants more commonly (Table 3). Also, they more commonly used

depressogenic medication(s) and had much higher scores in BDI. Vast majority of patients with suicidal ideation had BDI score > 11, interpreted as suggestive for depression (Table 3).

Multivariate analysis revealed that severity of depressive symptoms (as expressed in BDI score) and the use of potentially depressogenic medication(s) were independent determinants of suicidality among studied patients (Table 4). When continuous variable (BDI score) was replaced with a dichotomous one (i.e. presence or absence of depression reflected by BDI score > 11), the model of independent variables associated with suicidality comprised depression only (OR = 22.5; 95% CI = 5.2–97.5; $p < 0.00001$).

Table 3 – Comparison of variables related to depression between epileptic patients with and without suicidal ideation (univariate analysis). Data shown as n (%) or mean with standard deviation.

Variable	Suicidal ideation (n = 30)	No suicidal ideation (n = 271)	p-Value for the difference
History of depression	21 (70.0%)	20 (7.4%)	<0.001
Use of antidepressant(s)	20 (66.7%)	16 (5.9%)	<0.001
Use of potentially depression-inducing medication(s) ^a	8 (26.7%)	27 (10.0%)	0.007
Family history of depression	6 (20.0%)	38 (14.0%)	0.38
BDI total score	25.2 (9.1)	10.4 (8.6)	<0.001
BDI, cognitive-affective subscore	16.5 (6.2)	6.5 (5.7)	<0.001
BDI, somatic subscore	8.6 (4.0)	3.9 (3.5)	<0.001
BDI score > 11, suggestive for depression	28 (93.3%)	99 (36.5%)	<0.001

^a This category included β -blockers ($n = 27$), combinations of estrogen and progestogen ($n = 6$), corticosteroids ($n = 3$) and flunarizine ($n = 1$) (two patients used two of those drugs); BDI–Beck Depression Inventory.

Table 4 – Independent predictors of suicidal ideation among studied patients with epilepsy (logistic regression model with backward elimination).^a

Variable	Standard error	Wald statistics	p-Value	Odds ratio (95% confidence interval)
Beck Depression Inventory Score	0.025	36.06	<0.00001	1.16 (1.10–1.22) ^b
Use of depressogenic medications	0.545	4.17	0.04	3.04 (1.04–8.89)

^a χ^2 test = 58.4; $p < 0.000001$; percentage of appropriate classifications = 91.4%

^b Per one-point increase

The following variables were subsequently removed from the model with the backward elimination procedure: sex ($p = 0.98$), age at onset of epilepsy ($p = 0.98$), secondary generalized seizures ($p = 0.99$), polytherapy ($p = 0.97$), frequent seizures ($p = 0.67$); level of education ($p = 0.28$); vocational inactivity ($p = 0.38$), age ($p = 0.27$), marital status ($p = 0.40$), history of depression ($p = 0.13$), use of antidepressant(s) ($p = 0.19$), and use of clonazepam ($p = 0.11$).

4. Discussion

Our study revealed that depression, but not factors related to epilepsy itself, contributes to the occurrence of suicidal ideation among epileptic patients.

Death by suicide is reported much more commonly among epileptic patients than in general population. Rates of suicide in epilepsy vary enormously in relation to country, studied population and study design, but according to the analysis cited by Jones et al. [19] about 10% of all deaths in epileptic patients is due to suicide, which is in marked contrast with 1.1–1.2% rate in the general population. One-fourth of all subjects revealing suicidal ideation would ever make a plan to commit suicide, and about half of those who plan would make an attempt to do so [20]. Thus, the evaluation of suicidal thoughts and their relation to demographic and clinical variables seems to be a prerequisite for further prophylactic measures.

Evaluation of suicidal thoughts faces enormous difficulties and prospective studies notoriously failed to predict suicides despite fairly good evidence for specific correlates or risk factors for suicidality [21]. Several instruments were designed specifically to assess suicidal ideation, including Beck's Scale for Suicide Ideation (BSSI) [22] or Columbia Suicide Severity Rating Scale (CSSRS) [23], and therefore it may be argued that they should be used for that purpose. The common practice, however, is to use BDI as a single measure of suicidal ideation, as evidenced by longitudinal epidemiological studies [24], clinical trials [25], or studies aimed at the assessment of suicidality in epileptic patients [26]. Furthermore, Desseilles et al. [27] showed that the use of single 'suicidality' item from BDI might be a valid approach to assess the suicidal ideations when compared with BSSI. They concluded also that the use of self-reported questionnaire (BDI) was as useful as clinician-rated scale (Hamilton Scale for Depression) [27]. Accordingly, we believe that the use of BDI was in line with the purpose of our study which focused on the variables related to epilepsy rather than on more detailed description of suicidality among our patients.

Other screening methods can be reliably used in the same way, as recently evidenced by Mula et al. [28]. They studied the possible use of Neurological Disorders Depression Inventory for Epilepsy (NDDIE) as a suicidality screening instrument among 380 epileptic patients in three European countries and found that the single item 4 ('I'd be better off dead') had excellent psychometric properties with a good to excellent sensitivity and specificity against more elaborated Suicidality

Module of Mini International Neuropsychiatric Interview (MINI). Again, this finding confirms the potential utility of simple screening methods when evaluating epileptic patients for suicidality. Unfortunately, the Polish version of NDDIE has not been validated yet.

We have shown that current suicidal ideation can be found in about 10% of patients with epilepsy. This rate is very similar to other studies that used the same cross-sectional design. Hecimovic et al. [26] studied 193 American epileptic patients seen in tertiary clinic and reported suicidal ideation in 11.9% of them. The same rate (12.2%) was reported by Jones et al. [19]. It should be stressed, however, that the estimate provided by our findings is valid for the short period that preceded the survey. It may be reasonably argued that the prevalence and severity of suicidal ideation vary in longer intervals but it cannot be captured in a cross-sectional study. The potential confounding effect of postictal suicidal ideation on the prevalence of suicidal thoughts in general was also considered but we did our best to avoid it (BDI was assessed at least 3 days after the most recent seizure).

Univariate analysis revealed only minimal differences in demographic and clinical characteristics of patients with and without suicidal ideation. Firstly, patients who self-reported suicidal thoughts and wishes were slightly older. This feature is not limited to patients with epilepsy, however. Indeed, elderly patients are at the greatest risk for suicide in most countries [29]. Secondly, the percentage of women was slightly higher among patients with suicidality which may be viewed as a finding contradictory to the results of the studies in a general population [30]. Nevertheless, it is worthy to note that women with epilepsy are at slightly greater risk of suicide than men in population-based studies [1] which may be of importance regarding specific biological determinants of suicidality among women with epilepsy. Finally, patients with frequent seizures were more prevalent among subjects with suicidal thoughts. None of above-mentioned variables retained its significance in multivariate analysis, indicating that the difference between patients with and without suicidal ideation in regard of those determinants is very likely explained by the impact of depression in epileptic patients which was previously associated with female sex [4], older age [31] and higher frequency of seizures [32].

Depressive symptoms were the only independent determinant of suicidal thoughts and wishes in the studied cohort. BDI score higher than 11 (indicating clinical depression) was noted in 93.3% of patients with suicidal ideation and in 36.5% of other epileptic patients. Both somatic and cognitive-affective

subscores of BDI were also much greater in patients who reported suicidal thoughts. This result was expected, given the enormous literature that provides very strong link between psychiatric disorders and suicidality in general population [5], and among epileptic patients [19,26]. Recently, Christensen et al. [1] identified the highest risk of suicide in patients with epilepsy and concomitant psychiatric disease (OR = 13.7 when compared to general population) in population-based study. The detailed discussion of specific subtypes of depressive disorders within the cohort of patients reported here was published elsewhere [14]. It should be highlighted, however, that only one-quarter of epileptic patients diagnosed by us with depression was treated with antidepressant(s) at the time of the survey [33].

Also, the impact of depressogenic medications was more thoroughly reported in other paper that included vast majority of patients involved in the present analysis [33]. We interpret this finding as yet another confirmation of the overwhelming influence of depression on suicidal thoughts. It should be noted that the ad-hoc defined class of depressogenic medications did not include AED. None of AED was found to be a risk factor for suicide ideation in our study.

It may be surprising that we did not identify other independent determinants of suicidal thoughts among out patients with epilepsy but actually this is a prevailing conclusion from other recent studies on that topic [19,26,34]. Once the depression is taken into account in the predictive model, the significance of other variables (frequent seizures, AED polytherapy, advanced age or female sex) is minor or none. It is probably due to the fact that most of those factors increase also the risk of depression itself, and their prognostic role is 'included' in the effect of depression. Ideally, non-depressed patients with suicidal thoughts should be analyzed separately to further evaluate the potential impact of other factors. We were unable to do so, as only two patients in our cohort revealed suicidality without high BDI score.

An obvious link between epilepsy and depression and/or suicidality suggests also some common biological determinants of those manifestations. It has been shown recently that patients with suicidal ideation or behavior are at much greater risk of having epilepsy later in their life [8] which could be explained by shared pathomechanisms of both disorders. Several plausible abnormalities are thought to be involved, including dysfunction of serotonergic neurotransmission, increased activity of hypothalamic-pituitary-adrenal axis with resulting higher levels of serum cortisol, as well as an altered balance between GABA-ergic and glutamatergic neurotransmission (see [35] for review).

Some limitations of the study are acknowledged. The number of patients involved ($n = 301$) may be considered as small but it is actually larger than in most studies of the same design (i.e. $n = 193$ [26] or $n = 130$ [36]). Also, our study was performed among out-patients visiting epileptic clinic of the university hospital which limits the generalization of our findings. It should be stressed, however, that the majority of epileptic patients with epilepsy in Poland are managed by neurologists rather than family physicians and the spectrum of patients in our clinic is not limited to patients with refractory epilepsy (as evidenced by the detailed characteristics provided above). Longitudinal study with the long-term

follow-up would definitely provide more comprehensive insight into ever-changing mood disorders and suicidality among our patients. Yet, we consider our findings as exploratory ones and the multi-dimensional evaluation within the frame of the longitudinal study is planned.

Suicide is a potentially preventable outcome. Neurologists, very often involved in a long-term follow-up of patients with epilepsy, should take this opportunity to thoroughly assess the risk of suicide in their patients and to take precautionary measures, if required. Results of our study, along with other lines of evidence, stress the importance of mood disorders in suicidal ideations. Thus, they should be viewed as a potential target of any intervention aimed at decreasing the risk of suicide in patients with epilepsy.

In conclusion, suicidal ideations were revealed by about 10% of studied epileptic patients who visited tertiary center for epilepsy. Independent predictors of suicidality among studied patients included depression itself (expressed either as dichotomous variable or as a continuous one, i.e. BDI score > 11) and the use of potentially depressogenic medication.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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